CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-262/S-024

MEDICAL REVIEW(S)

JUN 30 1998

MEDICAL OFFICER'S FINAL LABELING REVIEW

NDA #20-262/SE1-024 **Submission Date: June 19, 1998 (v.2)**

Taxol for NSCLC **Review Date: June 29, 1998**
Applicant: Bristol-Myers Squibb

Attached is the final version of the label for TAXOL in combination with cisplatin in patients with non-small cell lung cancer (NSCLC). The sponsor's proposals and changes by the FDA reviewers (*italicized*) for the corresponding sections of the label are listed below. Please fax the following comments to the sponsor with the attachment.

CLINICAL STUDIES

1. Page 4:

To:

Reason: More accurate and useful information may be obtained from disease specific tables and discussions of adverse events compared to pooled tables which may dilute or exaggerate adverse events due to differences across patient populations.

In the Clinical Studies section, the above format was followed for all indications.

2. Page 7: When the two TAXOL-containing arms were pooled there was a significant survival advantage(p=0.049) compared to the cisplatin/etoposide arm.

Deleted.

3. (Page 7) Quality of Life:

To:

This section was edited with input from the reviewing statistician and DDMAC.

ADVERSE REACTIONS

1. Pages 11-13: Data in the following table based on the experience on 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in…

   Page 15, 17-19 Three multicenter trials were conducted in patients with advanced NSCLC and no prior chemotherapy….

2. Added after the table on page 15:

3. Note that the Adverse Events Section was grouped into

4. Page 18. Thrombocytopenia, Add:

5. Page 19: Neurologic, Add:

6. Page 19:

Omitted

OTHER CHANGES

Page 4 Analyses were performed as planned by bifactorial study design described in the protocol… There was a trend to longer time to progression for patients receiving the 3-hour vs. the 24-hour infusion: 4.0 months vs. 3.7 months (p=0.08).

To:

When the ovarian cancer dosing supplement was approved in 1994, data from the completed trial were inserted; however, the words describing the interim results were inadvertently retained. During the last revision of the label, Agency reviewers changed the wording from to a On further reflection, and after consultation with the Agency statisticians, the results by no means constitute a trend.

RECOMMENDATIONS

1. The supplement should be approved with the revised label.

2. We were unable to accept the Applicant's proposal for a pooled analysis of adverse reactions from combination treatment because:
   a. The pooled analysis obscures important differences due to dose and schedule.
   b. Data from the proposed analysis was not submitted for review.

3. The applicant should be requested to update the Adverse Events section to replace the current table of Adverse Events with a three column table combining data from all approved schedules but excluding Kaposi's Sarcoma: Taxol 175 mg/m^2/3 hours; Taxol 135 mg/m^2/3 hours; and Taxol 135 mg/m^2/24 hours + Cisplatin. If desired, a column with pooled data from 812 patients may still be retained, and the narrative section may still refer to this population. The incidence of febrile neutropenia should be added to this table. If toxicities attributed to cisplatin are omitted, the supplement should specify the incidence of such toxicities and provide rationale for their omission.

/S/ 6/31/98
Isagani Mario Chico, MD
Medical Reviewer

/S/ 6/30/98
Grant Williams, MD
Medical Team Leader

cc: NDA 20-262/024
HFD 150/Div File
HFD-150/Chico
HFD-150/ Spillman

SPILLMAN

APR -6 1998

MEDICAL OFFICER'S REVIEW OF AN NDA SUPPLEMENT
Taxol for Non-small Cell Lung Cancer

NDA # 20-262/SE1-024
Submission Date: **June 30, 1997**
Review completed: **April 6, 1998**
Sponsor: Bristol-Myers Squibb

TABLE OF CONTENTS

MEDICAL OFFICER'S REVIEW OF AN NDA SUPPLEMENT

NDA # 20-261/SE1-024

Submission Date: June 30, 1997
Review completed: March 31 , 1998

Sponsor: Bristol-Myers Squibb

GENERAL DRUG INFORMATION

Drug name: Taxol (paclitaxel) Injection
Generic name: Paclitaxel
Code name/Number: Taxol, NSC-125973, BMS-181339-01
Chemical Name: 20-Epoxy-1,2 ,4,7 ,10 ,13 -hexahydroxytax-11-en-9-one 10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine
Chemical Structure:

Chemical formula: $C_{47}H_{51}NO_{14}$

Molecular weight: 853.920

Pharmacological Category: Antineoplastic, antimicrotubule agent

Mechanism of Action

The biologic activity of taxol was originally ascribed to its ability to promote microtubulin formation. Taxol polymerizes tubulin into stable microtubules and induces the formation of stable microtubule bundles resulting in mitotic arrest. More recently, it has been demonstrated that taxol is effective in inducing bcl-2 phosphorylation and apoptosis in hormone therapy-resistant, bcl-2 positive, prostate cancer cells. Taxol has also been reported

to have anti-angiogenic activity directed at the endothelial cell response to angiogenic factors by inhibiting cell chemotaxis and invasiveness.

Proposed Indication

"Taxol is indicated for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy."

MANUFACTURING CONTROLS

Taxol (paclitaxel) is obtained via a semi-synthetic process from Taxus baccata. Taxol (paclitaxel) Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a non-aqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Taxol is available in 30 mg (5 ml) and 100 mg (16.7 ml) single-dose vials. Each ml of sterile non-pyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP. There are no manufacturing changes to the product for the indication being proposed in this supplemental NDA.

Pharmacokinetics

Following intravenous administration of paclitaxel, plasma concentrations decline in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusions at dose levels of 135 and 175 mg/m^2 were determined in a Phase 3 randomized study in ovarian cancer patients. It appeared that with the 24-hour infusion of taxol, a 30% increase in dose (135 mg/m^2 versus 175 mg/m^2) increased the C_{MAX} by 87%, whereas the AUC(0-α) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{MAX} and AUC(0-α) were increased by 68%. The mean apparent volume of distribution at steady state, with the 24-hour infusion of taxol, ranged from 227 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

Pharmacodynamics and Metabolism

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 μg/ml, indicate that between 89-98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15-275 mg/m^2 doses of taxol as 1, 6, or 24-hour infusions, mean (SD) values for cumulative urinary recovery of unchanged drug ranged from 1.3% (0.5%) to 12.6% (16.2%) of the dose, indicating extensive non-renal clearance. In five patients administered a 225 or 250 mg/m^2 dose of radiolabeled taxol as a 3-hour infusion, a mean (SE) of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6 -hydroxypaclitaxel, accounted for the balance. In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6 -hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6 ,3'-p-dihydroxypaclitaxel, by CYP3A4. In vitro, the metabolism of paclitaxel to 6-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporine, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found in vivo following normal therapeutic doses. Testosterone, 17 -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6 -hydroxypaclitaxel in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated. Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

III. CLINICAL BACKGROUND

Reviewer comment: *These notations "Reviewer comment" represent the FDA reviewer commentary and evaluation of the study. These are found throughout this NDA review to point out differences in the interpretation of study results, discrepancies in the data, or to emphasize certain aspects of the study that maybe relevant to the marketing approval and/or the approved labeling of taxol.*

Non-small cell lung cancers (NSCLC) accounts for 75% to 85% of all newly diagnosed lung cancer, which includes squamous cell carcinoma, adenocarcinoma, bronchoalveolar carcinoma, and large cell (anaplastic) carcinoma of the lung. It occurs mainly between the ages of 50 and 80 years and is associated with a high mortality. The estimated 5-year survival is 8% for patients who have disease that is regionally advanced and <1% for those with distant metastases. Survival is also poor for patients who relapse following initial surgical resection.

An international staging system for lung cancer is currently in use based upon the joint recommendation of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). This system defines stage III as patients with extrapulmonary extension of the disease (IIIA if resectable and IIIB if beyond the limits of resectability), and stage IV as patients with metastases to distant sites. Cumulative five year survival rates for stage IIIA patients is 15%, and less than 5% for stage III B and IV patients.

Chemotherapy provides a systemic approach to treatment; however, it is generally restricted to patients with metastatic and/or unresectable disease. Cisplatin is one of a number of active single agents for chemotherapy of advanced NSCLC, which has been reported to produce a 15 to 20% response rate. On the other hand, several combinations that include cisplatin have reached a response rate up to 50%; however, the duration of response has been short and the overall survival advantage not certain. In a meta-analysis by the Non-Small Cell Lung Cancer Cooperative Group of 1190 patients with advanced NSCLC enrolled in 11 randomized trials, platinum-containing regimens improved the 1-year survival rate to approximately 23% as compared to 18% for patients on best supportive care alone. This translated into an increase in median survival from approximately 4.0 months in the best supportive care group to approximately 6.3 months in patients receiving a platinum-containing regimen. Compared to best supportive care, cisplatin based regimens reduced the risk of death by 27% (hazard ratio 0.73, 95% C.I. 0.63 to 0.85, $p<0.0001$).

Since chemotherapy in this setting is not curative, the extension of survival must be weighed against the potential toxicity of treatment. Because of this reason, combinations containing cisplatin and a podophyllotoxin such as etoposide and teniposide have been used because of relatively mild and non-overlapping toxicity, and the potential for synergism.

Vinorelbine (navelbine) is approved as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced non-small cell lung cancer (NSCLC). Efficacy data from the two pivotal clinical trials are summarized in the following table:

Table 1. Pivotal Trials- Navelbine

Treatment Arm	European Study (n=612)			North American Study (n=211)	
	Navelbine /Cisplatin	Vindesine/ Cisplatin	Navelbine	5-FU/ leucovorin	Navelbine
Response Rate	28%	19%	14%	12%	3%
Median Survival (weeks)	40	32	31	22	30
1-Year Survival (%)	35%	27%	30%	16%	24%

Several subsequent randomized trials showed the superiority in efficacy of the combination of cisplatin + vinorelbine over either single agents.

Table No. 2
Randomized Trials of Cisplatin and Vinorelbine in NSCLC
(from sec 8/10, vol 1, p. 19)

Regimen (Author)	Number of Patients	Response Rate (CR+PR)	Median survival (months)
Cisplatin+vinorelbine vs. vinorelbine (LeChevalier)	412	30 14 (p<0.001)	10 7.8 (p<0.04)
Cisplatin+vinorelbine vs. vinorelbine (Depierre)	240	43 16 (p=0.0001)	8.3 8.0 p=NS
Cisplatin+vinorelbine vs. cisplatin (Wozniak)	432	25 10 (p=0.0001)	7.0 6.0 (p=0.001)

New anticancer agents (paclitaxel, irinotecan, docetaxel and gemcitabine) have shown efficacy as single agents in NSCLC and are currently being tested in randomized studies as single agents and in combination with cisplatin.

Combination chemotherapy with cisplatin in NSCLC results in higher response rates compared to single-agent therapy. Overall survival is probably not improved by single agent chemotherapy but has been shown with combination chemotherapy in several randomized clinical trials. However, the contribution to overall survival should also be examined against the potential for increased toxicity and possible effect on patient's quality of life. Overall, a new drug being evaluated should be superior to the control regimen since standard chemotherapy for advanced NSCLC has not been established.

Prolongation of time to tumor progression in advanced NSCLC has often been used as a measure of a treatment's relative effectiveness. This is particularly useful if prolongation of survival is also demonstrated. However, a treatment that delays tumor progression may not necessarily prolong survival. In the setting of an adequate and well-controlled randomized clinical trial, a prolongation in time to progression associated with clear improvement in quality of life or disease related symptoms may be considered a suitable surrogate for demonstrating clinical benefit.

The ideal setting possible for approval of new drugs for advanced NSCLC would be the demonstration of superiority in overall survival without compromise in quality of life and/or increased toxicity, since there is no available "standard treatment" for NSCLC. This is especially important if the drug will be used for first-line treatment of patients who are not amenable to surgery and/or radiotherapy.

Development of Taxol in NSCLC

The initial phase II trials of taxol in NSCLC were done in 1990 by ECOG and MD Anderson Cancer Center and employed a 24-hour infusion schedule of taxol at 250 mg/m^2 every three weeks. Objective response rates were greater than 20% and one-year survival about 40%, but with significant myelosuppression. The starting dose of taxol was later lowered to 200 mg/m^2. In 1993, the first phase II trials in NSCLC were started in Europe using the three hour iv infusion schedule at a dose of 200 to 225 mg/m^2 which turned out to be less myelosuppressive but with similar objective response and survival rates. Subsequent phase II trials progressively abandoned the long infusion schedule in favor of shorter schedules that became more attractive in the palliative setting.

The clinical trials utilizing taxol as a single agent provide evidence of efficacy of this agent against NSCLC. When taxol was combined with platinum agents (cisplatin or carboplatin), the objective response rates increased to 42% and 38%, respectively. No definite effect of infusion duration on the response rates were observed. The response rate for single agent taxol using a 24-hour infusion was 23% and 35% for the 3-hour infusion. For taxol with cisplatin, the response rate was 28% using a 24-hour infusion and 41% using a 3-hour infusion. Taxol has been studied using other schedules such as one hour, weekly three hours,

96 hours as single agent and in combination with radiotherapy and other chemotherapy agents.

Two of the three phase III studies submitted utilized what was thought at the time of study inception as the "best" combination chemotherapy control arm. Study 139-165 used the combination of cisplatin and etoposide in comparison to cisplatin plus a 24-hour infusions of taxol divided into a high dose arm with G-CSF support and a low dose taxol arm. Study 139-103 compared cisplatin plus teniposide with a three hour infusion of taxol with cisplatin.

The selection of the proper platinum-containing combination has been guided both by efficacy and safety considerations. Combinations using cisplatin and a podophyllotoxin (etoposide or teniposide) have been adopted because of relatively mild toxicity and the potential for thrapeutic synergism.

Pivotal Regimens of Cisplatin and Podophyllotoxins: Randomized Trials in Non-Small Cell Lung Cancer
(from Sec. 1.2.2, vol. 86.2, p.18)

Regimen	No. of Patients	CR+PR(%)	Median Survival (months)	Author
Cisplatin+teniposide vs. teniposide	225	22 6 (p<0.001)	7.2 5.9 (p=0.008)	Splinter
Cisplatin+ etoposide vs. etoposide	216	26 7 (p<0.005)	8.0 6.0 NS	Rosso
Cisplatin + etoposide vs. cisplatin	93	30 4 (p<0.01)	8.8 4.5 (p<0.02)	Crino
Cisplatin+etoposide vs. cisplatin	162	26 19 NS	5.5 6.5 NS	Klatersky

In an ECOG randomized trial of four active chemotherapy regimens, a response rate of 20% was observed for cisplatin/etoposide; however, a subsequent analysis of two randomized trials involving 893 patients demonstrated that treatment with cisplatin/etoposide resulted in the highest one year survival rate (25%) among several chemotherapy regimens. As a result of this analysis, ECOG selected cisplatin/etoposide as the reference regimen for subsequent randomized trials.